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A strategy for structuring and reporting a read-across prediction of toxicity ☆

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ABSTRACT

Category formation, grouping and read across methods are broadly applicable in toxicological assessments and may be used to fill data gaps for chemical safety assessment and regulatory decisions. In order to facilitate a transparent and systematic approach to aid regulatory acceptance, a strategy to evaluate chemical category membership, to support the use of read-across predictions that may be used to fill data gaps for regulatory decisions is proposed. There are two major aspects of any read-across exercise, namely assessing similarity and uncertainty. While there can be an over-arching rationale for grouping organic substances based on molecular structure and chemical properties, these similarities alone are generally not sufficient to justify a read-across prediction. Further scientific justification is normally required to justify the chemical grouping, typically including considerations of bioavailability, metabolism and biological/mechanistic plausibility. Sources of uncertainty include a variety of elements which are typically divided into two main issues: the uncertainty associated firstly with the similarity justification and secondly the completeness of the read-across argument. This article focuses on chronic toxicity, whilst acknowledging the approaches are applicable to all endpoints. Templates, developed from work to prepare for the application of new toxicological data to read-across assessment, are presented. These templates act as proposals to assist in assessing similarity in the context of chemistry, toxicokinetics and toxicodynamics as well as to guide the systematic characterisation of uncertainty both in the context of the similarity rationale, the read across data and overall approach and conclusion. Lastly, a workflow for reporting a read-across prediction is suggested.

1. Introduction and problem formulation

Legislative requirements for registration and safety assessment of chemicals have demonstrated the need for a new way of thinking to obtain toxicological information without resorting to animal testing. The grouping of substances allowing read-across of toxicity is a valuable method to obtain such information and potentially has a number of regulatory applications. The underlying philosophy of read-across is that substances which are similar in chemical structure will have similar properties and thereby, have similar toxicokinetic and toxicodynamic properties. Therefore, experimentally-derived toxicological properties from one

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substance, often referred to as the source chemical, can be read across to fill the data gap for a second substance, the target chemical, which has a similar chemical structure and for which a toxicology study may be lacking.

Despite the fact that read-across has been used for several years, a number of challenges remain. For instance, when applying read-across to make a prediction of toxicity, a number of questions arise, for which answers may be difficult to arrive at or to document; including:

(1) Can a robust group of chemicals (often referred to as a chemical category) be formed to include the target chemical?
(2) Is the category formed relevant for the toxicology of the endpoint under assessment?
(3) Are there appropriate toxicology studies of high enough quality for the source chemical(s) to allow a meaningful read-across?
(4) What is the uncertainty and is it acceptable to use the read across prediction to fill the data gap for a specific regulatory purpose?

To begin to address these questions a flexible strategy for developing and reporting a read-across prediction has been created. The strategy focuses on the two main elements of any read-across estimation, namely assessing (1) the similarity between target(s) and source substance(s) and (2) the uncertainties in the read-across process and ultimate prediction. While the standards for accepting a read-across prediction can vary between regulatory agencies, a good basis is the standard required for filling a REACH registration information requirement (EC, 2006). Conceptually, this means, for example, that in the context of a safety assessment for a complete set of results it should be possible to read-across the findings of a 28-/90-day repeated-dose oral rat toxicity study on the source substance(s) to the target substance(s). As such, the aim of the read-across is to provide a prediction(s) that is (more or less) equivalent to the omitted standard animal study and hence be acceptable for regulatory purposes.

The intent of this document is to establish a strategy which may be used to conduct and document read-across predictions for data gap filling. As such, it provides guiding principles for developing read-across predictions for discrete organic compounds. Where possible, emphasis has been placed on undertaking and describing the read-across prediction in the best manner to facilitate regulatory acceptance. This document represents, in part, discussions in and progress made in the European Commission and Cosmetics Europe funded SEURAT-1 Cluster (www.seurat-1.eu). As such, the primary focus of this document is directed towards read-across predictions for chronic toxicity, or improving the possibility to read-across from repeat dose toxicity tests. However, in order to achieve this aim, the document draws upon current expertise and knowledge from other toxicological endpoints and the information, templates and work plans contained herein are generally applicable to all read-across scenarios and endpoints.

In order to facilitate regulatory acceptance, a read-across prediction needs to be justified in all aspects. Briefly, the justification of a read-across prediction needs to be robust, reliable and easily explicable. Key principles of similarity need to be clearly documented and, where possible, supported by scientific literature and data. Sources of uncertainty need to be identified and accommodated; these can typically be divided into two main types: (1) the uncertainty associated with the justification of similarity between the source and target structures, and (2) the uncertainty associated with the application of the particular read-across exercise.

Whilst no consensus has been reached by stakeholders and users, there is growing agreement that when read-across is applied to make predictions to fulfil information requirements, this must be done on an endpoint-by-endpoint basis, i.e. for the particular toxicology study to be predicted. This approach to apply to endpoints individually is due, even when there is an over-arching category hypothesis, to different applicability domains, different source chemicals and/or different Weights-of-Evidence (WoE) which may apply to making predictions for different endpoints. Obviously, there will be occasions where one or more endpoints will be closely related and knowledge may be transferable, thus allowing read-across arguments to build, partially, on each other.

It is generally agreed that the acceptability of a read-across prediction relies on the explanation of the similarity which forms the basis of the read-across, as well as the description of the type and degree of uncertainty associated with the particular read-across. Therefore, it is important to address these two elements in a transparent and consistent manner. The use of templates or work plans facilitates the elucidation of the transparency and consistency in read-across. Existing templates or reporting formats for read-across vary in detail, however, it is generally agreed that they aim to:

(1) Describe the rationale for the similarity between the source and target chemical in a transparent manner.
(2) Document the logic and data leading to the read-across prediction so that, if required, it can subsequently be recreated.
(3) Describe the uncertainties in the prediction; specifically separating the uncertainties in data and definition of similarity from procedural uncertainty.
(4) Clarify the roles of any endpoint specific and/or endpoint non-specific factors affecting the assessment.

2. Background

Read-across is an alternative method for filling data gaps based on an analogue or chemical category approach (van Leeuwen et al., 2009). It is the process of assessing a toxic endpoint of an untested substance (i.e., target chemical) based on the results for the same endpoint for a tested substance (i.e., source chemical) considered to be "similar" in the context of structure, properties and/or activities (Dimitrov and Mekenyan, 2010). It is recognised that forming a chemical category and data gap filling by interpolation within the category, especially for hazard assessments, is not a new concept (OECD, 2014a). However, greater emphasis has now been placed on the resultant read-across prediction due to legislative pressure, especially within Europe, and especially for classification and labelling, and risk assessment. Currently, there is growing interest in several national Governmental regulatory agencies to establish best practices for conducting and evaluating read-across within the context of, and to enable, regulatory decisions. Published exercises and case studies using the OECD QSAR Toolbox (cf. Enoch et al., 2013) have demonstrated that category-based read-across can be used to establish that a substance is associated with potentially hazardous properties. However, it is more difficult to show that a substance is not potentially hazardous. In order to address this issue, the more recent literature has identified some of the challenges which need to be taken into account when preparing a read-across justification (cf. Patlewicz et al., 2013a, 2014); specifically, case studies have described the process to create a read-across prediction increasing the likelihood of regulatory acceptance (cf. Ball et al., 2014).

Much guidance on grouping of chemicals and read-across is already available (ECETOC, 2012; ECHA, 2009, 2011; OECD, 2007, 2011, 2014a) and the key strategic documents have been summarised in Table 1.4 of Cronin (2013a). This is a fast moving field and the formation of chemical categories, or the grouping of molecules, especially to allow for the filling of data gaps by read-across,